# $Beta_2$ Adrenergic Agonists – Short-Acting Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

| Drug Name | Manufacturer | Reversible Bronchospasm | | Prevention of Exercise Induced Broncho-spasm | Chronic Obstructive Pulmonary Disease (COPD) | Age of Use (years) |
|---|---|---|---|---|---|---|
| | | Prevention and Treatment | Relief | | | |
| **Short-Acting Inhalation Agents** | | | | | | |
| albuterol DPI (ProAir RespiClick®)[1] | Teva | X | – | X | – | >12 |
| albuterol HFA (ProAir®, Proventil® HFA, Ventolin® HFA)[2,3,4] | Proventil HFA by Merck Sharp & Dohme | X | X | X | – | ≥4 |
| | Ventolin HFA by GlaxoSmithKline | | | | | |
| | ProAir HFA by Teva | | | | | |
| albuterol inhalation solution[5,6] | generic | – | X | – | – | ≥2 |
| albuterol low-dose inhalation solution (AccuNeb®)[7] | generic, Mylan Specialty | – | X | – | – | children 2–12 years and adolescents |
| levalbuterol HFA (Xopenex® HFA)[8] | Sunovion | X | – | – | – | ≥4 |
| levalbuterol inhalation solution (Xopenex®)[9] | generic, Sunovion | X | – | – | – | ≥6 |
| **Oral Agents** | | | | | | |
| albuterol oral syrup[10] | generic | – | X | – | – | ≥2 |
| albuterol oral tablets[11] | generic | – | X | – | – | ≥6 |
| metaproterenol oral syrup[12] | generic | X | – | – | X | ≥6 |
| metaproterenol oral tablets[13] | generic | X | – | – | – | ≥6 |
| terbutaline tablets[14] | generic | – | X | – | X | ≥12 |

DPI=dry powder inhaler, HFA=hydrofluoroalkane

## OVERVIEW

Beta$_2$-agonist bronchodilators are the medications of choice for the treatment and prevention of bronchospasm associated with asthma and prophylaxis of exercise-induced bronchospasm (EIB) in adults and children. They are also used in the treatment of chronic obstructive pulmonary disease (COPD).[15]

In some patients with chronic asthma, a clear distinction between asthma and COPD may be difficult. Differing features between asthma and COPD include: the onset of asthma is usually in childhood,

while onset of COPD is in mid-life; asthma symptoms vary from day to day and time during the day, COPD symptoms progress slowly; allergy, rhinitis and/or eczema are usually present in asthma patients. There may be a genetic link with asthma; COPD is due to tobacco smoke, indoor/outdoor and occupational pollutants.[16]

## Asthma

Medications to treat asthma are classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to maintain asthma control. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve symptoms.[17]

Short-acting beta$_2$-agonists (SABAs) have a rapid onset or action and are useful for temporary relief of bronchoconstriction and the accompanying acute symptoms such as wheezing, chest tightness, and cough. Short-acting agents have not been shown to be as beneficial as the long-acting controller medications for asthma management.[18] Also, increased use of reliever medications is a warning of deterioration in asthma control that indicates a need to reassess treatment.

In 2007 the National Asthma Education and Prevention Panel (NAEPP) of the National Heart Lung and Blood Institute (NHLBI) released a summary of the third report of the Expert Panel (EPR-3) that emphasizes the importance of asthma control, and identifies asthma severity as the intrinsic intensity of the disease process. The EPR-3 advises of the need to first assess severity as the basis of initial therapy and then assess control to adjust therapy. The NAEPP recommends that SABAs are the drug of choice for treating acute asthma symptoms and exacerbations and for preventing EIB. Regularly scheduled, daily, chronic use of a SABA is not recommended. Use of a short-acting agent greater than two days per week for symptom relief is indicative of inadequate asthma control; anti-inflammatory medication should be started or intensified.

The 2015 Global Initiative for Asthma (GINA) report centers on the diagnosis and management of asthma in the clinical practice setting.[19] The group defines asthma as a heterogeneous disease, usually characterized by chronic airway inflammation. A cyclic treatment plan is emphasized to allow for continued assessment, adjustment, and review of response. GINA categorizes asthma severity based on the level of treatment required to control symptoms. Mild asthma is well-controlled with as-needed SABA or low dose inhaled corticosteroid (ICS). Moderate and severe asthma is controlled with low to moderate dose ICS and long-acting beta$_2$ agonists (LABAs). GINA provides a five-step treatment approach which offers flexibility to step up treatment if control is lost or to step down treatment when asthma is controlled. In each step reliever medication should be provided for quick relief as needed.

## COPD

Bronchodilator medications are central to the symptomatic management of COPD.[20,21,22,23] They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance.[24] Regular bronchodilation with these drugs does not modify the decline of function in mild COPD or the prognosis of the disease.[25] The principal bronchodilator treatments are beta$_2$-agonists, anticholinergics, and theophylline. These may be given either as monotherapy or in combination. While short-acting beta$_2$-agonists can be used on an as-needed basis in mild COPD, regular treatment with a long-acting agent is required as the disease progresses.[26]

The 2015 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state beta$_2$-agonist bronchodilators are among the principal treatments for symptomatic management of COPD.[27]

Treatment objectives are the immediate relief of symptoms and the risk reduction of future adverse health events. Previously, COPD severity was classified as stages, based on forced expiratory volume in one second ($FEV_1$) measurement; however, current guidelines state that the $FEV_1$ is an unreliable marker of the severity of breathlessness, exercise limitation, and health status impairment for an individual patient. The classification system was modified and now uses a grading system of airflow limitations based on the ratio $FEV_1$/forced vital capacity (FVC) and is as follows: GOLD 1 – Mild; GOLD 2 – Moderate; GOLD 3 – Severe; and GOLD 4 – Very Severe. A fixed ratio, post bronchodilator $FEV_1/FVC < 0.7$ confirms persistent airflow limitation and a diagnosis of COPD. It is recognized that the use of the fixed ratio may lead to more frequent diagnoses of COPD in older adults with mild COPD as the normal process of aging affects lung volumes and flows, and may lead to under-diagnosis in adults younger than 45 years. The current guidelines incorporate a combined assessment using the GOLD grade in conjunction with a symptomatic assessment and a patient's exacerbation history. Symptoms are assessed using the modified British Medical Research Council (mMRC) or COPD Assessment Test (CAT) to determine if the patient has less symptoms (mMRC grade 0-1 or CAT < 10) or more symptoms (mMRC grade ≥ 2 or CAT ≥ 10). The risk of exacerbations is assessed using either the GOLD population based risk assessment or the number of exacerbations within the last 12 months (≤ 1 indicates low risk while ≥ 2 indicates high risk). If the two risk assessments differ, the higher risk assessment is used. The classification system is divided into four groups:

**Group A: Low Risk, Less Symptoms** – Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year AND mMRC grade 0-1 or CAT < 10

**Group B: Low Risk, More Symptoms** – Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year AND mMRC grade ≥2 or CAT ≥ 10

**Group C: High Risk, Low Symptoms** – Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation) and/or ≥2 exacerbation per year AND mMRC grade 0-1 or CAT < 10)

**Group D: High Risk, More Symptoms** – Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation) and/or ≥2 exacerbation per year AND mMRC grade ≥ 2 or CAT ≥ 10

The advantage of the combined approach is that it demonstrates the complexity of COPD better than the GOLD population-based risk classification system and facilitates individualized therapy. Short-acting bronchodilators are used as needed and are considered first-line treatment for patients in Group A. Long-acting bronchodilators are recommended in patients with more advanced disease, either alone or in combination with other agents depending on disease severity.

## Devices

In 2005, the American College of Chest Physicians (ACCP) and the American College of Allergy, Asthma, and Immunology (ACAAI) issued joint evidence-based guidelines for selecting aerosol delivery devices for use in asthma or COPD.[28] The authors performed a systematic review of randomized controlled trials comparing the efficacy and adverse effects of treatment using nebulizers versus pressurized metered-dose inhalers (MDIs) with or without a spacer/holding chamber versus dry powder inhalers (DPIs) as delivery systems for $beta_2$-agonists, anticholinergic agents, and corticosteroids in several commonly encountered clinical settings and patient populations. The authors conclude that devices used for the delivery of bronchodilators and steroids can be equally efficacious. The 2015 GINA update states DPIs may be used to deliver SABA as an alternative to pressurized MDI and spacer during

worsening asthma or exacerbations; however, the available studies did not include patients with severe acute asthma.[29]

The 2015 GINA update also maintains that inhaled therapy constitutes the cornerstone of asthma treatment in children five years of age and younger.[30] Similar improvement in lung function has been shown in patients with mild to moderate asthma treated with a SABA administered via an MDI and a spacer as compared to a nebulizer. Since the dose may vary considerably from one spacer device to another, a spacer that has documented efficacy in young children is recommended. The choice of inhaler device for use in children should be based on the child's age and capability. The preferred delivery system is a pressurized MDI with a valved spacer with a face mask for children younger than four years of age and a mouthpiece for most children four to five years old. Nebulizers should be reserved for the minority of children who cannot be taught effective use of a spacer device. Factors such as arthritis, muscle weakness, impaired vision and inspiratory flow should be considered in choosing an inhaler device for older patients.

## PHARMACOLOGY[31,32,33,34,35]

Beta-agonists stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity, especially from mast cells. $Beta_2$-agonists relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, COPD, or bronchiectasis. Bronchodilation may additionally facilitate expectoration. [36,37]

Although there are both $beta_1$ and $beta_2$ receptors in the heart, the latter are more predominant in the lungs, where they serve as the primary adrenergic receptors in bronchial smooth muscle. In order to reduce cardiac toxicities (e.g., tachyarrhythmias), the use of $beta_2$ specific agonists is preferred in the treatment of bronchospasm. This has minimized the use of less specific and less safe agents such as epinephrine (Primatene Mist® – withdrawn from the U.S. market as of December 31, 2011) and isoproterenol (Isuprel®). Racepinephrine, an alpha and beta agonist, marketed as Asthmanefrin™, has emerged on the over-the-counter (OTC) market as a chlorofluorocarbon (CFC)-free replacement to the former Primatene Mist®. The FDA has regulated the strengthening of the final monograph and labeling of OTC bronchodilator products – those containing ephedrine, epinephrine, racephedrine, and racepinephrine hydrochloride – as of January 2012.[38] To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.

Since the signing of the Montreal Protocol in 1987, new propellants, such as non-ozone-depleting hydrofluoroalkane (HFA), for use in pressurized MDIs have been developed. Several randomized, double-blind, placebo-controlled, crossover studies have shown that albuterol MDIs pressurized by HFA are equivalent, in terms of efficacy and tolerability, to the original CFC albuterol MDIs in both adolescents and adults.[39,40,41,42] This equivalence was shown for both the treatment and prophylactic (EIB) indications of albuterol. The FDA completed its phase-out of albuterol inhalers using ozone-depleting CFCs as propellants on December 31, 2008. Patients who used albuterol inhalers containing CFCs were switched to HFA containing MDIs. The final phase of U.S. market elimination for the remaining inhalers using CFCs, metaproterenol MDI (Alupent®) and pirbuterol (Maxair® Autohaler®), was concluded on June 14, 2010 and December 31, 2013 respectively.

## PHARMACOKINETICS[43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58]

| Drug | Relative ß$_2$ Specificity | Onset of Action (minutes) | Duration of Action (hours) |
|---|---|---|---|
| **Short-Acting Inhalation Agents** | | | |
| albuterol DPI (ProAir RespiClick) | ß$_2$ >> ß$_1$ | 5 – 15 | 3 – 6 |
| albuterol HFA (ProAir HFA, Proventil HFA, Ventolin HFA) | ß$_2$ >> ß$_1$ | 5.4 – 8.2 | 3 – 6 |
| albuterol inhalation solution (generic, AccuNeb) | ß$_2$ >> ß$_1$ | 5 – 15 | 3 – 6 |
| levalbuterol HFA (Xopenex HFA) | ß$_2$ >> ß$_1$ | 5 – 10 | 3 – 6 |
| levalbuterol inhalation solution (Xopenex) | ß$_2$ >> ß$_1$ | 10 – 17 | 5 – 8 |
| **Oral Agents** | | | |
| albuterol syrup, tablets | ß$_2$ >> ß$_1$ | 30 | 4 – 8 |
| metaproterenol syrup, tablets | ß$_2$ > ß$_1$ | 30 | ≥4 |
| terbutaline tablet | ß$_2$ >> ß$_1$ | 30 | 4 – 8 |

## CONTRAINDICATIONS/WARNINGS[59,60,61,62,63,64,65,66,67,68,69]

No specific contraindications exist for the short-acting beta$_2$-agonists (SABAs).

Warnings that are common to the SABAs include: paradoxical bronchospasm (can be life threatening), cardiovascular effects (e.g., effects on blood pressure and pulse rate), excessive dose and usage, acute deterioration of asthma and use of anti-inflammatory agents (e.g., corticosteroids). SABAs should be used with caution in patients with heart disease, seizure disorder, diabetes, and hyperthyroidism.

There have been rare reports of seizures in patients receiving terbutaline; seizures did not recur in these patients after the drug was discontinued.

The 2015 GINA update states high usage of SABAs is a risk factor for asthma exacerbations; furthermore, excessive usage (e.g., more than 200 doses/month) is a risk factor for asthma-related death.[70]

## DRUG INTERACTIONS[71,72,73,74,75,76,77,78,79,80,81]

### Monoamine Oxidase (MAO) Inhibitors and Tricyclic Antidepressants

All beta$_2$-agonists should be administered with extreme caution to patients being treated with MAO inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because these agents may potentiate the action of adrenergic agonists on the cardiovascular system. Allow two weeks after discontinuation of MAO inhibitors before initiating therapy with agents in this category.

### Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not

normally be treated with beta-blockers. However, under certain circumstances, such as prevention of myocardial re-infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma or COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

## Diuretics

Electrocardiogram (ECG) changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of $beta_2$-agonists with non-potassium-sparing diuretics. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

## Digoxin

Mean decreases of 16 and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for ten days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear; nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol and levalbuterol.

## ADVERSE EFFECTS[82,83,84,85,86,87,88,89,90,91,92,93,94,95,96]

| Drug | Headache | Nausea/ Vomiting | Nervousness | Palpitations | Tachycardia | Tremor |
|---|---|---|---|---|---|---|
| **Short-Acting Inhalation Agents** | | | | | | |
| albuterol DPI (ProAir RespiClick) | reported | nr | nr | reported | nr | reported |
| albuterol HFA (ProAir HFA ,Proventil HFA, Ventolin HFA,) | 7 – 20 | 7 – 10 | 7 | <3 | <3 – 7 | 2 – 7 |
| albuterol inhalation solution (generic, AccuNeb) | reported | 1.7/0.9 | reported | reported | nr | reported |
| levalbuterol HFA (Xopenex HFA) | reported | 10.5 | reported | reported | reported | reported |
| levalbuterol inhalation solution (Xopenex) | 7.6 – 11.9 | <2 | 2.8 – 9.6 | reported | 2.7 – 2.8 | 0 – 6.8 |
| **Oral Agents** | | | | | | |
| albuterol syrup | 4 | <1 – 2 | 9 – 15 | <1 | 1 – 2 | 10 |
| albuterol tablets | 7 | 2 | 20 | 5 | 5 | 20 |
| metaproterenol syrup | 1.1 | 1.3 | 4.8 | <1 | 6.1 | 1.6 |
| metaproterenol tablets | 7 | 0.8 - 3.6 | 20.2 | 3.8 | 17.1 | 16.9 |
| terbutaline tablets | 7.8 – 10 | 1.3 – 10 | <5 – 31 | ≤23 | 1.3 – 3 | <5 – 38 |

Adverse effects data are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive.

nr = not reported.

## SPECIAL POPULATIONS[97,98,99,100,101,102,103,104,105,106]

### Pediatrics

Most of the short-acting beta-agonists (SABAs) have been studied in pediatric patients and shown to be safe and effective in children as young as two years of age. There is insufficient clinical data to establish safety and efficacy of terbutaline sulfate; therefore, it is not recommended for patients under the age of 12 years. Additionally, ProAir RespiClick is intended for patients 12 years of age and older.

### Pregnancy

There are no adequate and well-controlled studies of these agents in pregnant women. Terbutaline is Pregnancy Category B. All of the SABAs are Pregnancy Category C. They should only be used during pregnancy if the potential benefit justifies the potential risk.

### Geriatrics

These agents have not been studied in a geriatric population. Special caution should be observed when using these agents in elderly patients with coexisting conditions like impaired renal function and cardiovascular disease that could be adversely affected by this class of drug.

### Hepatic Impairment

No dosage adjustments are needed in hepatically impaired patients who use albuterol, albuterol HFA, or levalbuterol.

### Renal Impairment

Exercise caution and monitor patients with renal impairment who use albuterol, albuterol HFA, or levalbuterol. No special monitoring or dosage adjustments are needed in patients with renal impairment who use metaproterenol.

## DOSAGES[107,108,109,110,111,112,113,114,115,116,117,118,119,120,121]

| Drug | Usual Adult Dosage | Usual Pediatric Dose | Availability |
|---|---|---|---|
| **Short-Acting Inhalation Agents** | | | |
| albuterol DPI (ProAir RespiClick) | 2 inhalations every 4 to 6 hrs as needed<br>Prevention of EIB: 2 inhalations 15 to 30 minutes prior to exercise | Do not use in patients under 12 years of age | 117 mcg per actuation from the device reservoir<br>108 mcg per actuation from the mouth piece |
| albuterol HFA (Proventil HFA, Ventolin HFA, ProAir HFA) | 2 inhalations every 4 to 6 hrs as needed<br><br>Prevention of EIB: 2 inhalations 15 to 30 minutes prior to exercise | 2 inhalations every 4 to 6 hrs as needed<br><br>Prevention of EIB: 2 inhalations 15 to 30 minutes prior to exercise | 90 mcg per actuation<br>(Ventolin HFA and ProAir HFA have dose counters attached to the actuator) |
| albuterol inhalation solution (generic, AccuNeb) | 2.5 mg every 6 to 8 hrs as needed | 0.63 to 2.5 mg 4 to 4 times daily as needed | generic:<br>2.5 mg/3 mL,<br>5 mg/mL<br><br>AccuNeb or low-dose generic:<br>0.63 mg/3 mL,<br>1.25 mg/3 mL |
| levalbuterol HFA (Xopenex HFA) | 2 inhalations every 4 to 6 hrs as needed | 2 inhalations every 4 to 6 hrs as needed | 45 mcg per actuation |
| levalbuterol inhalation solution (Xopenex) | 0.63 to 1.25 mg 3 times daily | 0.31 to 0.63 mg 3 times daily | 0.31 mg/3 mL,<br>0.63 mg/3 mL,<br>1.25 mg/3 mL |
| **Oral Agents** | | | |
| albuterol oral syrup | 2 to 4 mg every 6 to 8 hrs | 0.1 to 0.2 mg/kg every 8 hrs | 2 mg/5 mL |
| albuterol oral tablets | 2 to 4 mg every 6 to 8 hrs | 2 mg every 6 to 8 hrs | Immediate Release: 2 mg, 4 mg<br>Extended Release: 4 mg, 8 mg |
| metaproterenol oral syrup | 20 mg 3 to 4 times daily | 10 mg 3 to 4 times daily | 10 mg/5 mL |
| metaproterenol oral tablets | 20 mg 3 to 4 times daily | Age 6 – 9 years old or weight < 60lbs:<br>10 mg 3 to 4 times daily<br>Age > 9 years old or weight > 60lbs:<br>20 mg 3 to 4 times daily | 10 mg, 20 mg |
| terbutaline tablets | 2.5 to 5 mg 3 times daily | 2.5 mg 3 times daily | 2.5 mg, 5 mg |

# CLINICAL TRIALS

## Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

## Asthma

***albuterol inhalation solution (Proventil, Ventolin) versus levalbuterol inhalation solution (Xopenex)***

In a randomized, double-blind, placebo-controlled, crossover study, 20 adults with mild-to-moderate asthma received single doses of levalbuterol inhalation solution (0.31, 0.63, and 1.25 mg) and albuterol inhalation solution (2.5 mg).[122] All doses of active treatment produced a significantly greater degree of bronchodilation (measured by change in forced expiratory volume in 1 second [$FEV_1$]) than placebo, and there were no significant differences between any of the active treatment arms. The bronchodilator response of levalbuterol 1.25 mg and albuterol 2.5 mg showed similar efficacy over the 6 hour evaluation period, except for a slightly longer duration of action after administration of levalbuterol 1.25 mg. Systemic beta adrenergic adverse effects were observed with all active doses. Levalbuterol 1.25 mg produced a slightly higher rate of systemic beta adrenergic adverse effects than the albuterol 2.5 mg dose. This study was funded by the manufacturer of levalbuterol.

A multicenter, randomized, double-blind, placebo- and active-controlled study was conducted in 338 children with mild-to-moderate asthma.[123] Following a 1-week placebo run-in period, subjects were randomized to nebulized levalbuterol 0.31 or 0.63 mg, albuterol 1.25 or 2.5 mg, or placebo given 3 times daily for 3 weeks. Of the 338 patients who were randomized, 316 patients completed the study. Efficacy, measured by mean peak change in $FEV_1$, was demonstrated for all active treatment regimens compared with placebo ($p<0.001$). The onset and duration of effect of levalbuterol are consistent with those of albuterol.

A randomized, double-blind, controlled trial was conducted in children age 1 to 18 years (n=482) in the emergency department (ED) and inpatient asthma care unit of an urban tertiary children's hospital.[124] Patients received a nebulized solution of either 2.5 mg racemic albuterol or 1.25 mg levalbuterol every 20 minutes (maximum 6 doses). Patients admitted to the asthma care unit were treated in a standardized fashion by using the same blinded drug assigned in the ED. Hospitalization rate was the primary outcome. Hospitalization rate was significantly lower in the levalbuterol group (36%) than in the racemic albuterol group (45%, p=0.02). The adjusted relative risk of admission in the racemic group

compared with the levalbuterol group was 1.25 (95% confidence interval (CI), 1.01 to 1.57). Hospital length of stay was not significantly shorter in the levalbuterol group (levalbuterol, 44.9 hours; racemic albuterol, 50.3 hours; p=0.63). No significant adverse events occurred in either group.

A randomized, double-blind, controlled trial was conducted in 99 children aged 6 to 17 years in the emergency department (ED). Inclusion criteria included a history of asthma, ED presentation consistent with asthma exacerbation, and an initial $FEV_1$ of less than 70% predicted.[125] Patients were randomized to receive via continuous nebulization either 7.5 mg of albuterol or 3.75 mg of levalbuterol over a 1 hour period, in addition to standard asthma therapies. Spirometry and asthma scoring were performed at the end of the first hour, and a second hour-long nebulization with the same drug was administered if deemed necessary. Spirometry and asthma scoring were again performed and recorded. As a second, optional part of the study, baseline serum albuterol levels were collected on some patients prior to treatment. Baseline characteristics were similar except that the albuterol group had a higher baseline asthma score. Children in the albuterol group had a greater improvement in their $FEV_1$ (p=0.043) as well as in their asthma scores (p=0.01) after 1 hour of continuous treatment compared to the levalbuterol group. The greater improvement in asthma scores was maintained after the second hour of continuous therapy in the albuterol group (p=0.008) but not for $FEV_1$ measurements (p=0.57). There were no differences between groups for changes in heart rate, respiratory rate, oxygen saturation, or rates of admission. The authors concluded that at the doses used, albuterol appears to be superior to levalbuterol with respect to changes in $FEV_1$ and asthma score. There was no significant difference between the drugs with respect to admission rates or side-effect profile.

## COPD

### *albuterol MDI (Proventil, Ventolin) versus formoterol DPI (Foradil) versus salmeterol DPI (Serevent) in COPD*

A cross-over, randomized, double-blind, placebo-controlled study was carried out on 20 patients with COPD.[126] Patients underwent pulmonary function testing and dyspnea evaluation in basal condition and at 5, 15, 30, 60, and 120 minutes after bronchodilator (albuterol metered-dose inhaler (MDI), formoterol dry powder inhaler [DPI], or salmeterol DPI) or placebo administration. The results indicated that in COPD patients with decreased baseline inspiratory capacity, there was a much greater increase of inspiratory capacity after bronchodilator administration, which correlated closely with the improvement of dyspnea sensation at rest. On average, formoterol DPI elicited the greatest increase in inspiratory capacity than the other bronchodilators used.

## Meta-Analyses

A systematic review of pertinent randomized, controlled, clinical trials was undertaken using MEDLINE, EmBase, and the Cochrane Library databases to determine if a difference in efficacy and adverse effects exists among the various aerosol delivery devices (metered-dose inhalers [MDIs] versus dry powder inhalers [DPIs] versus nebulizers) used in the management of asthma and COPD exacerbations.[127] A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested $beta_2$-agonists) proved to have useable data. None of the pooled meta-analyses showed a significant difference among devices in any efficacy outcome in any patient group for each of the clinical settings that were investigated. The adverse effects that were

reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation.

## SUMMARY

The 2015 GINA guidelines for asthma, recommend inhaled short-acting beta$_2$-agonist (SABA) as medications of choice for quick relief of asthma symptoms and bronchoconstriction including in acute exacerbations, and for exercise-induced bronchoconstriction. Due to its rapid onset of action, relative lack of adverse systemic effects, and availability of multiple dosage forms, albuterol remains the most commonly used SABA bronchodilator. Merck (Proventil HFA), Teva (ProAir HFA) and GlaxoSmithKline (Ventolin HFA) produce albuterol inhalers using HFA propellant. Teva (ProAir RespiClick) manufactures albuterol inhalers using dry powder meters.

In general, oral dosage forms of albuterol are less utilized than the inhaled forms due to systemic beta-adrenergic stimulation of the former, especially in patients sensitive to these effects, such as those with cardiovascular disease. Metaproterenol is neither as beta$_2$ selective nor as long acting as albuterol, and therefore should not be considered for first-line therapy. Another beta$_2$-agonist, terbutaline, is more beta$_2$ selective than metaproterenol but is available only as oral tablets. The short duration of action of terbutaline reduces its value in the treatment of bronchoconstriction.

Levalbuterol (Xopenex) is the R-enantiomer form of albuterol. Levalbuterol inhalation solution has similar efficacy to albuterol inhalation solution when given in equivalent doses. In addition, an HFA-propelled inhaler containing the enantiomer of albuterol is available as levalbuterol HFA (Xopenex HFA). There are no significant differences in adverse effects between albuterol and levalbuterol formulations.

## REFERENCES


1 ProAir RespiClick [package insert]. Horsham, PA; Teva; March 2015.
2 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2012.
3 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2014.
4 ProAir HFA [package insert]. Horsham, PA; Teva; May 2012.
5 Albuterol sulfate inhalation solution 0.083% [package insert]. Corona, CA; Watson Pharma, Inc.; April 2014.
6 Albuterol sulfate inhalation solution 0.5% [package insert]. Tampa, FL; Bausch & Lomb Inc.; July 2014.
7 AccuNeb inhalation solution [package insert]. Napa, CA; Mylan Specialty L.P.; January 2013.
8 Xopenex HFA [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; September 2013.
9 Xopenex inhalation solution [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; August 2014.
10 Albuterol sulfate syrup [package insert]. Sellersville, PA; Teva; April 2011.
11 Albuterol sulfate tablets [package insert]. Morgantown, WV; Mylan Pharmaceuticals; January 2010.
12 Metaproterenol sulfate syrup [package insert]. Spring Valley, NY; Silarx Pharmaceuticals Inc.; January 2001.
13 Metaproterenol sulfate tablets [package insert]. Spring Valley, NY; PAR Pharmaceutical Co. Inc; July 2010.
14 Terbutaline [package insert]. Philadelphia, PA; Global Pharmaceuticals; June 2001.
15 The GOLD Guidelines: Executive summary: global strategy for the diagnosis, management, and prevention of COPD 2015. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf. Accessed September 2, 2015.
16 The GOLD Guidelines: Executive summary: global strategy for the diagnosis, management, and prevention of COPD 2015. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf. Accessed September 2, 2015.
17 Global strategy for asthma management and prevention. Global Initiative for Asthma (GINA) 2015. Available at: http://www.ginasthma.org/Guidelines/guidelines-resources.html. Accessed September 2, 2015.
18 National Asthma Education and Prevention Program Expert Panel Report: Guidelines for the diagnosis and management of asthma. Expert panel report 3. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed September 9, 2015.
19 Global strategy for the diagnosis and management of asthma in children five years and younger. Global Initiative for Asthma (GINA) 2015. Available at: http://www.ginasthma.org/Guidelines/guidelines-resources.html. Accessed September 2, 2015.
20 Vathenen AS, Britton JR, Ebden P, et al. High-dose inhaled albuterol in severe chronic airflow limitation. Am Rev Respir Dis. 1988; 138:850-855.
21 Gross NJ, Petty TL, Friedman M, et al. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study. Am Rev Respir Dis. 1989; 139:1188-1191.

22 Chrystyn H, Mulley BA, Peake MD. Dose response relation to oral theophylline in severe chronic obstructive airways disease. BMJ. 1988; 297:1506-1510.
23 Higgins BG, Powell RM, Cooper S, et al. Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. Eur Respir J. 1991; 4:415-420.
24 Wilson DH, Wakefield MA, Steven ID, et al. "Sick of smoking": evaluation of a targeted minimal smoking cessation intervention in general practice. Med J Aust. 1990; 152:518-521.
25 The GOLD Guidelines: Executive summary: global strategy for the diagnosis, management, and prevention of COPD 2015. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf. Accessed September 2, 2015.
26 The GOLD Guidelines: Executive summary: global strategy for the diagnosis, management, and prevention of COPD 2015. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf. Accessed September 2, 2015.
27 The GOLD Guidelines: Executive summary: global strategy for the diagnosis, management, and prevention of COPD 2015. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf. Accessed September 2, 2015.
28 Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest. 2005; 127:335-371.
29 Global strategy for asthma management and prevention. Global Initiative for Asthma (GINA) 2015. Available at: http://www.ginasthma.org/Guidelines/guidelines-resources.html. Accessed September 2, 2015.
30 Global strategy for the diagnosis and management of asthma in children five years and younger. Global Initiative for Asthma (GINA) 2015. Available at: http://www.ginasthma.org/Guidelines/guidelines-resources.html. Accessed September 2, 2015.
31 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2012.
32 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2014.
33 ProAir RespiClick [package insert]. Horsham, PA; Teva; March 2015.
34 ProAir HFA [package insert]. Horsham, PA; Teva; May 2012.
35 Xopenex inhalation solution [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; August 2014.
36 Sharma G. Asthma: treatment & medication. Available at: http://emedicine.medscape.com/article/1000997-treatment. Accessed September 9, 2015.
37 Kleinschmidt P. Chronic obstructive pulmonary disease and emphysema: treatment & medication. Available at: http://emedicine.medscape.com/article/807143-treatment. Accessed September 9, 2015.
38 Department of Health and Human Services: Food and Drug Administration. 21 CFR Parts 201 and 341: Labeling for bronchodilators to treat asthma; cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use. Available at: http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/pdf/2011-18347.pdf. Accessed September 9, 2015.
39 Lumry W, Noveck R, Weinstein S, et al. Switching from Ventolin CFC to Ventolin HFA is well tolerated and effective in patients with asthma. Ann Allergy Asthma Immunol. 2001; 86:297-303.
40 Langley SJ, Sykes AP, Batty EP, et al. A comparison of the efficacy and tolerability of single doses of HFA 134a albuterol and CFC albuterol in mild-to-moderate asthmatic patients. Ann Allergy Asthma Immunol. 2002; 88:488-93.
41 Shapiro G, Bronsky E, Murray A, et al. Clinical comparability of Ventolin formulated with hydrofluoroalkane or conventional chlorofluorocarbon propellants in children with asthma. Arch Pediatr Adolesc Med. 2000; 154:1219-1225.
42 Hawksworth RJ, Sykes AP, Faris M, et al. Albuterol HFA is as effective as albuterol CFC in preventing exercise-induced bronchoconstriction. Ann Allergy Asthma Immunol. 2002; 88:473-7.
43 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2014.
44 ProAir HFA [package insert]. Horsham, PA; Teva; May 2012.
45 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2012.
46 Proventil inhalation solution [package insert]. Kenilworth, NJ; Schering Corporation; February 2002.
47 AccuNeb inhalation solution [package insert]. Napa, CA; Mylan Specialty L.P.; January 2013.
48 ProAir RespiClick [package insert]. Horsham, PA; Teva; March 2015.
49 Xopenex inhalation solution [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; August 2014.
50 Xopenex HFA [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; September 2013.
51 Proventil Repetabs [package insert]. Kenilworth, NJ; Schering Corporation; October 2000.
52 Proventil syrup [package insert]. Kenilworth, NJ; Schering Corporation; June 1997.
53 Metaproterenol sulfate syrup [package insert]. Spring Valley, NY; Silarx Pharmaceuticals Inc.; January 2001.
54 Metaproterenol sulfate tablets [package insert]. Spring Valley, NY; PAR Pharmaceutical Co. Inc; July 2010.
55 Terbutaline [package insert]. Philadelphia, PA; Global Pharmaceuticals; June 2001.
56 Clinical Pharmacology. Available at: http://www.clinicalpharmacology-ip.com/default.aspx. Accessed September 16, 2015.
57 Albuterol sulfate inhalation solution 0.083% [package insert]. Corona, CA; Watson Pharma, Inc.; April 2014.
58 Albuterol sulfate inhalation solution 0.5% [package insert]. Tampa, FL; Bausch & Lomb Inc.; July 2014.
59 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2014.
60 ProAir HFA [package insert]. Horsham, PA; Teva; May 2012.
61 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2012..
62 Proventil inhalation solution [package insert]. Kenilworth, NJ; Schering Corporation; February 2002.
63 AccuNeb inhalation solution [package insert]. Napa, CA; Mylan Specialty L.P.; January 2013.
64 Xopenex inhalation solution [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; August 2014.
65 Xopenex HFA [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; September 2013.
66 Metaproterenol sulfate tablets [package insert]. Spring Valley, NY; PAR Pharmaceutical Co. Inc; July 2010.
67 ProAir RespiClick [package insert]. Horsham, PA; Teva; March 2015.
68 Albuterol sulfate inhalation solution 0.083% [package insert]. Corona, CA; Watson Pharma, Inc.; April 2014.
69 Albuterol sulfate inhalation solution 0.5% [package insert]. Tampa, FL; Bausch & Lomb Inc.; July 2014.
70 Global strategy for asthma management and prevention. Global Initiative for Asthma (GINA) 2015. Available at: http://www.ginasthma.org/Guidelines/guidelines-resources.html. Accessed September 2, 2015.

71 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2014.
72 ProAir HFA [package insert]. Miami, FL; Teva; August 2010.
73 Proventil HFA [package insert]. Whitehouse Station, NJ; 3M Drug Delivery System; June 2012.
74 Proventil inhalation solution [package insert]. Kenilworth, NJ; Schering Corporation; February 2002.
75 AccuNeb inhalation solution [package insert]. Napa, CA; Mylan Specialty L.P.; January 2013.
76 Xopenex inhalation solution [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; August 2014.
77 Xopenex HFA [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; July 2012.
78 Metaproterenol sulfate syrup [package insert]. Spring Valley, NY; Silarx Pharmaceuticals Inc.; January 2001.
79 Metaproterenol sulfate tablets [package insert]. Spring Valley, NY; PAR Pharmaceutical Co. Inc; July 2010.
80 Albuterol sulfate inhalation solution 0.083% [package insert]. Corona, CA; Watson Pharma, Inc.; April 2014.
81 Albuterol sulfate inhalation solution 0.5% [package insert]. Tampa, FL; Bausch & Lomb Inc.; July 2014.
82 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2014.
83 ProAir HFA [package insert]. Miami, FL; Teva; August 2010.
84 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2012.
85 Proventil inhalation solution [package insert]. Kenilworth, NJ; Schering Corporation; February 2002.
86 AccuNeb inhalation solution [package insert]. Napa, CA; Mylan Specialty L.P.; January 2013.
87 ProAir RespiClick [package insert]. Horsham, PA; Teva; March 2015.
88 Xopenex inhalation solution [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; August 2014.
89 Xopenex HFA [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; September 2013.
90 Proventil syrup [package insert]. Kenilworth, NJ; Schering Corporation; June 1997.
91 Proventil Repetabs [package insert]. Kenilworth, NJ; Schering Corporation; October 2000.
92 Metaproterenol sulfate syrup [package insert]. Spring Valley, NY; Silarx Pharmaceuticals Inc.; January 2001.
93 Metaproterenol sulfate tablets [package insert]. Spring Valley, NY; PAR Pharmaceutical Co. Inc; July 2010.
94 Terbutaline [package insert]. Philadelphia, PA; Global Pharmaceuticals; June 2001.
95 Albuterol sulfate inhalation solution 0.083% [package insert]. Corona, CA; Watson Pharma, Inc.; April 2014.
96 Albuterol sulfate inhalation solution 0.5% [package insert]. Tampa, FL; Bausch & Lomb Inc.; July 2014.
97 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2014.
98 ProAir HFA [package insert]. Horsham, PA; Teva; May 2012.
99 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2012.
100 Proventil inhalation solution [package insert]. Kenilworth, NJ; Schering Corporation; February 2002.
101 AccuNeb inhalation solution [package insert]. Napa, CA; Mylan Specialty L.P.; January 2013.
102 Xopenex inhalation solution [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; August 2014.
103 Xopenex HFA [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; September 2013.
104 Metaproterenol sulfate tablets [package insert]. Spring Valley, NY; PAR Pharmaceutical Co. Inc; July 2010.
105 Albuterol sulfate inhalation solution 0.083% [package insert]. Corona, CA; Watson Pharma, Inc.; April 2014.
106 Albuterol sulfate inhalation solution 0.5% [package insert]. Tampa, FL; Bausch & Lomb Inc.; July 2014.
107 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2014.
108 ProAir HFA [package insert]. Horsham, PA; Teva; May 2012.
109 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2012.
110 Proventil inhalation solution [package insert]. Kenilworth, NJ; Schering Corporation; February 2002.
111 AccuNeb inhalation solution [package insert]. Napa, CA; Mylan Specialty L.P.; January 2013.
112 ProAir RespiClick [package insert]. Horsham, PA; Teva; March 2015.
113 Xopenex HFA [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; September 2013.
114 Xopenex inhalation solution [package insert]. Marlborough, MA; Sunovion Pharmaceuticals Inc; August 2014.
115 Proventil syrup [package insert]. Kenilworth, NJ; Schering Corporation; June 1997.
116 Proventil Repetabs [package insert]. Kenilworth, NJ; Schering Corporation; October 2000.
117 Metaproterenol sulfate syrup [package insert]. Spring Valley, NY; Silarx Pharmaceuticals Inc.; January 2001.
118 Metaproterenol sulfate tablets [package insert]. Spring Valley, NY; PAR Pharmaceutical Co. Inc; July 2010.
119 Terbutaline [package insert]. Philadelphia, PA; Global Pharmaceuticals; June 2001.
120 Albuterol sulfate inhalation solution 0.083% [package insert]. Corona, CA; Watson Pharma, Inc.; April 2014.
121 Albuterol sulfate inhalation solution 0.5% [package insert]. Tampa, FL; Bausch & Lomb Inc.; July 2014.
122 Handley DA, Tinkelman D, Noonan M, et al. Dose-response evaluation of levalbuterol verses racemic albuterol in patients with asthma. J Asthma. 2000; 37:319-27.
123 Milgrom H, Skoner DP, Bensch G, et al. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. J Allergy Clin Immunol. 2001; 108:938-45.
124 Carl JC, Myers TR, Kirchner HL, et al. Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. J Pediatr. 2003; 143(6):731-6.
125 Wilkinson M, Bulloch B, Garcia-Filion P, et al. Efficacy of racemic albuterol versus levalbuterol used as a continuous nebulization for the treatment of acute asthma exacerbations: a randomized, double-blind, controlled trial. J Asthma. 2011; 48(2): 188-93.
126 Di Marco F, Milic-Emili J, Boveri B, et al. Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD. Eur Respir J. 2003; 21:86-94.
127 Dolovich MB, Ahrens RC, Hess DR, et al. Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest. 2005; 127:335-371.